Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting
April 7, 2016

FDA Introductory Remarks

NDA 207999: Obeticholic Acid

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Obeticholic acid (OCA)

- Analog of the naturally occurring bile acid chenodeoxycholic acid (CDCA)

- Oral administration as a daily dose ≤ 10 mg

- "Treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA."

OCA Clinical Program in PBC

- Primary Biliary Cirrhosis/Cholangitis is a rare disease
- Clinical program:
  - two phase 2 trials (dose selection)
  - one phase 3 trial
- Primary efficacy endpoint in phase 2:
  - % change in alkaline phosphatase (ALP)
- Primary efficacy endpoint in phase 3 (composite):
  - alkaline phosphatase and total bilirubin

Primary Efficacy Endpoint - Phase 3 Clinical Trial

o Primary efficacy endpoint (Month 12):

   o alkaline phosphatase (<1.67 X ULN) AND

   o total bilirubin (≤ULN) AND

   o alkaline phosphatase (≥15% reduction from baseline)

o Endpoint selection leveraged data from the PBC Study Group:

   o elevated ALP and total bilirubin were linked to risk of death/liver transplantation in a <u>diverse</u> PBC patient population

Lammers WL et al. Gastroenterology 2014; 147; 1338-49

PBC Patient Population in the Phase 3 Clinical Trial

o **At least 1** of the following qualifying biochemistry values:

- ALP $\geq$ 1.67 X ULN

- Total bilirubin > ULN but < 2X ULN

o Favored enrollment of patients with early stage PBC:

- elevated ALP (99%)

- normal bilirubin ($\sim$ 90%)

- normal albumin ($\sim$99%)

FDA Statistical Analyses of the Global PBC Study Group

- Multi-national, multi-center registry study

- ~ 5,000 adult PBC patients with longitudinal alkaline phosphatase information and clinical outcome data (death or liver transplant)

- FDA accessed selected data and identified a subset of patients with characteristics <u>similar</u> to those in the phase 3 obeticholic acid trial

- FDA assessed the relationship between the changes in ALP values and clinical outcomes (death/liver transplantation) and identified ALP thresholds that may predict clinical response

ALP and PBC Clinical Trials with OCA

- ALP is **not** an assessment of a **clinical outcome** (i.e., how a patient feels, functions or survives)

- ALP is a **pharmacodynamic/response biomarker** (shows that a biological response has occurred as a consequence of an intervention - obeticholic acid)

- ALP is **not** a **validated surrogate endpoint** (i.e., it is not a substitute for a direct measure of how a patient feels, functions, or survives)

- ALP is a **candidate surrogate endpoint** (i.e., it is still under evaluation for its ability to predict clinical benefit)

BEST (Biomarkers, EndpointS, and other Tools) at:
http://www.ncbi.nlm.nih.gov/books/NBK326791/

FDA Discussion Points for the Advisory Committee

- Discuss if ALP is a surrogate endpoint reasonably likely to predict clinical benefit in the treatment of early stage Primary Biliary Cirrhosis/Cholangitis

- Do the data support accelerated approval of OCA for the treatment of PBC, based on its effect on alkaline phosphatase?

- OCA dosing recommendations

- Use of OCA as monotherapy

- Dosing in patients with hepatic impairment

- Efficacy across the entire spectrum of PBC

- Continued dosing in patients who do not meet response criteria

- Phase 4 confirmatory study design

Global PBC Study Group Data Analysis for the Clinical Trial Population

Min Min, PhD

Division of Biometrics III

Office of Biostatistics

CDER, FDA

April 7, 2016

Background

- The Applicant submitted three efficacy trials to support the accelerated approval of OCA in treating patients with PBC.

- Following FDA's advice, the Applicant collaborated with the Global PBC Study Group to investigate whether alkaline phosphatase (ALP) and total bilirubin (TB) could be used as biomarkers reasonably likely to predict clinical outcome (liver transplant or death).

- The Applicant leveraged the findings from the Global PBC Group Project (Lammers, 2014) to support the use of ALP and TB as biomarkers in the phase 3 pivotal trial (Trial 747-301).

Rationale for Re-analysis of Global PBC Data

One inclusion criterion for the trial 747-301 was that subjects must have a baseline ALP ≥ 1.67xULN and/or TB >ULN.

	Global PBC Data (N=4845)	Trial 747-301 (N=216)
Early disease stage	2040 (42%)	195 (90%)
Moderately advanced disease stage	730 (15%)	21 (10%)
Advanced disease stage	259 (5%)	0 (0%)
Total bilirubin (>ULN)	974 (20%)	18 (8%)

The population studied in the trial 747-301 is not directly comparable to the Global PBC data.

Statistical Analysis Plan

Total Number of Patients in Global PBC Data
n=4845 (1118 events; 23%)

Early disease stage

UDCA use

Baseline ALP at least 1.67xULN

Comparable Subset of Global PBC Data
n=909 (131 events; 14%)

25%

75%

Model Selection
n=227

Exploration of Potential Cutoffs
n=682

Subgroup Analyses
n=909

Ten Random Splits (10 splits)

5-fold Cross Validation (5-fold)
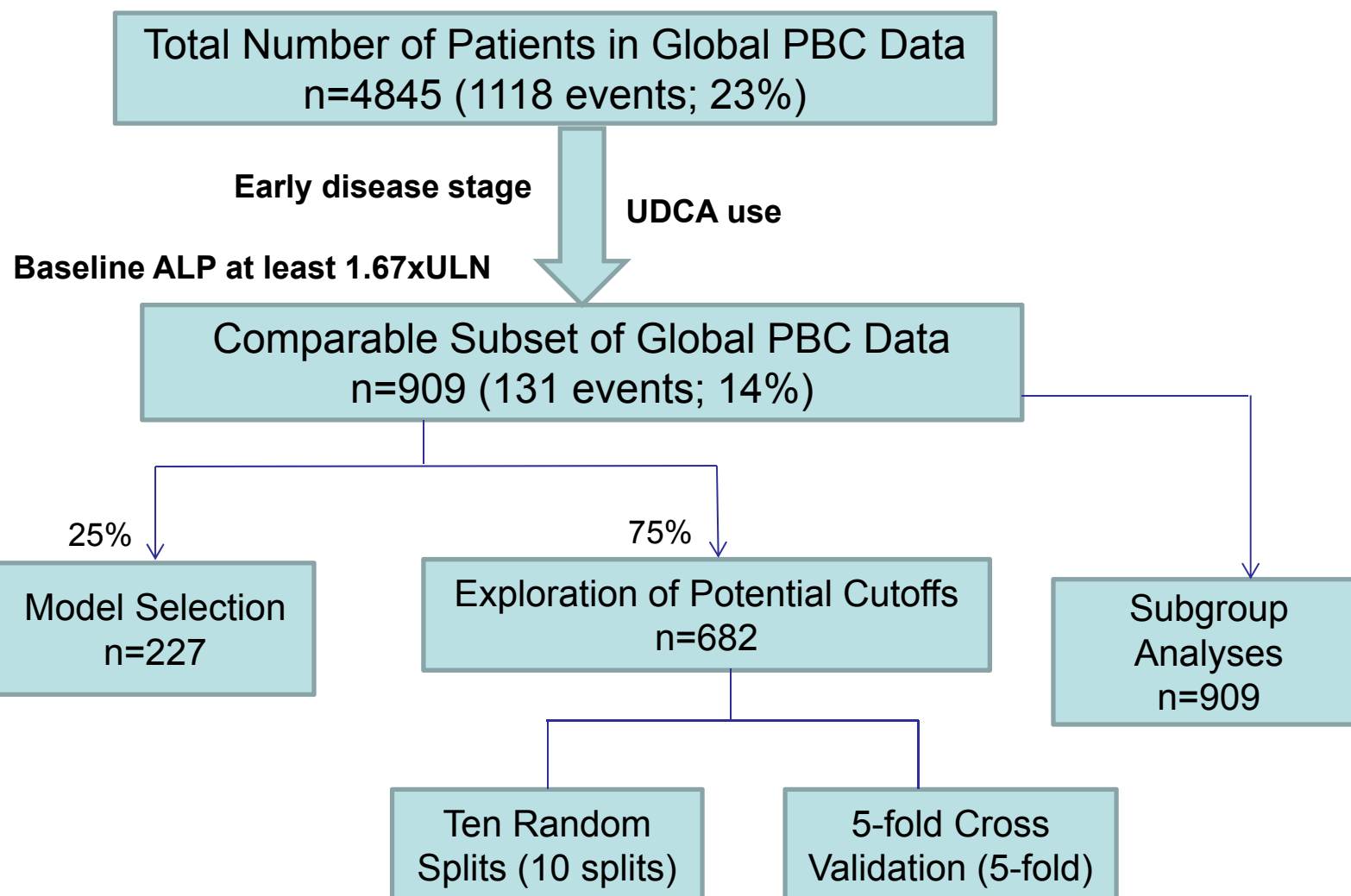
ALP at Month 12 Appears to be an Important Predictive Factor

Five Covariates:

- age
- age at diagnosis
- year of diagnosis
- region
- duration of PBC

Two Types of ALP at Month 12:

- absolute (ALP12)
- percentage change from baseline (PGALP12)

The model with factors:
age, baseline ALP raw lab values, and PGALP12 was chosen to predict death or liver transplant

Akaike information criterion (AIC) range	Model (different combinations of 5 covariates)
(224.851*, 232.604)	With PGALP12 and baseline ALP raw values
(249.604, 259.618)	Without PGALP12 and baseline ALP raw values

*The selected model had the smallest AIC value (shown in blue, above)

C-statistic

The C-statistic is commonly used to demonstrate the predictability of a biomarker.

Pr_1	Pr_{-1}	add to correct	add to N
0.8	0.2	+1	+1
0.6	0.7	+0	+1
0.5	0.5	+0.5	+1
0.3	0.1	+1	+1
0.9	0.7	+1	+1

c = correct / N = 3.5/5 = 0.7

ROC Plot

True positive Rate

$c > 0.5$

AUC

45° line
(coin toss)
$c = 0.5$

False positive Rate
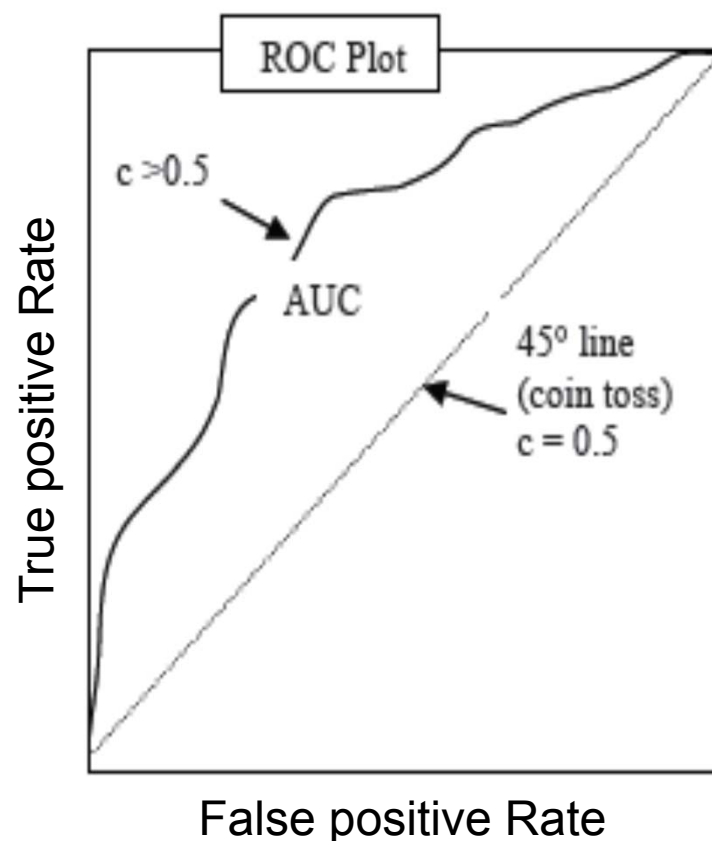
Source: Hermansen, Evaluating Predictive Models: Computing and Interpreting the c Statistic paper 143-2008

Cutoff Exploration Based on Both Absolute and Percentage Change of ALP

Cutoffs (ALP at Month 12)	C-statistic (mean)			
	10 splits (training)	10 splits (testing)	5-fold (training)	5-fold (testing)
<1.67xULN & ≥15%↓ (Applicant's cutoff)	0.64	0.68	0.65	0.68
<1.67xULN & ≥40%↓	0.65	0.68	0.65	0.66
<2.0xULN & ≥15%↓	0.68	0.70	0.69	0.70
<2.0xULN & ≥40%↓	0.69	0.70	0.69	0.70

Our Finding: (<2.0xULN & ≥15%↓) and (<2.0xULN & ≥40%↓) performed numerically better than the Applicant's cutoff and (<1.67xULN & ≥40%↓)
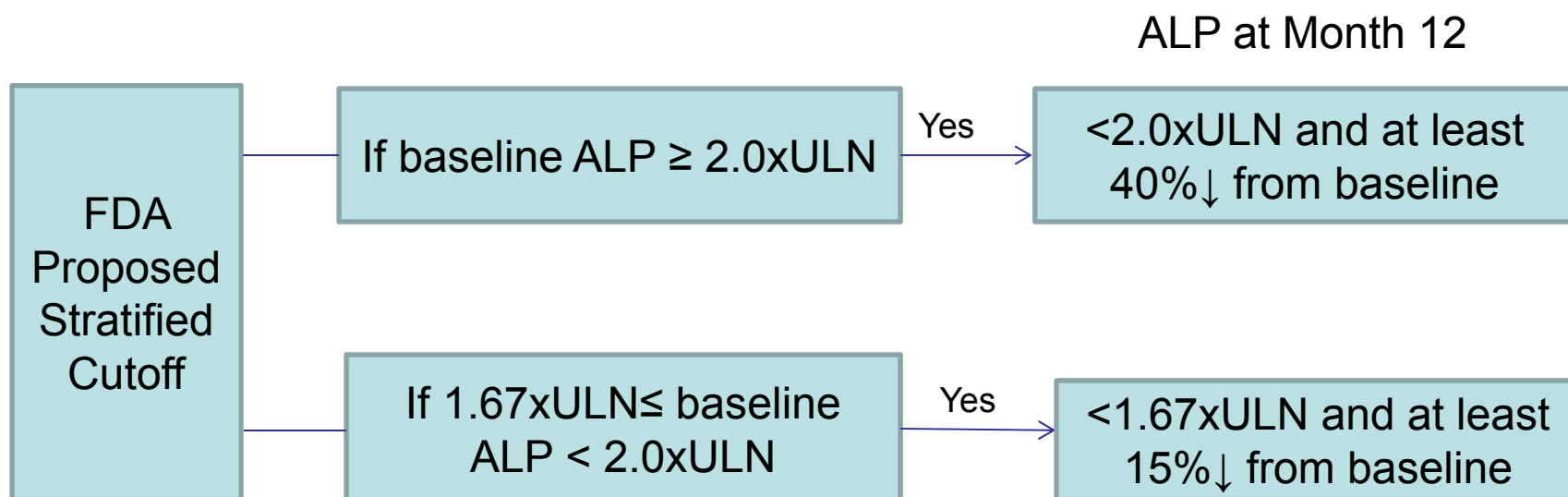
Seventeen Potential Cutoffs

5 Absolute Cutoffs				
<1.0xULN	<1.67xULN	<1.76xULN	<2.0xULN	<3.0xULN
4 Percentage Cutoffs				
≥15%↓	≥30%↓		≥40%↓	≥60%↓
4 Combined Cutoffs				
<1.67xULN & ≥15%↓	<1.67xULN & ≥40%↓		<2.0xULN & ≥15%↓	<2.0xULN & ≥40%↓

ALP at baseline	4 Stratified Cutoffs			
Stratum 1 (≥ 2.0xULN)	<2.0xULN & ≥15%↓	<2.0xULN & ≥ 40%↓	<2.0xULN & ≥15%↓	<2.0xULN & ≥40%↓
Stratum 2 (≥ 1.67xULN and < 2.0xULN)	<1.67xULN & ≥15%↓	<1.67xULN & ≥40%↓	<1.67xULN & ≥40%↓	<1.67xULN & ≥15%↓

Exploration of Potential Cutoffs
(Based on 10 Splits)

Cutoffs	C-statistic (mean)	Hazard Ratio (mean)	Hazard Ratio 95% CI
10 Splits (training)			
<1.67xULN & ≥15%↓	0.64	1.82	(1.06, 3.13)
(<1.67xULN & ≥15%↓) or (<2.0xULN & ≥40%↓)	0.69	2.29	(1.33, 3.97)
10 Splits (testing)			
<1.67xULN & ≥15%↓	0.68	2.42	(1.08, 5.51)
(<1.67xULN & ≥15%↓) or (<2.0xULN & ≥40%↓)	0.70	2.54	(1.15, 5.69)

Exploration of Potential Cutoffs
(Based on 5-fold)

Cutoffs	C-statistic (mean)	Hazard Ratio (mean)	Hazard Ratio 95% CI
5-fold (training)			
<1.67xULN & ≥15%↓	0.65	1.95	(1.19, 3.21)
(<1.67xULN & ≥15%↓) or (<2.0xULN & ≥40%↓)	0.69	2.32	(1.42, 3.80)
5-fold (testing)			
<1.67xULN & ≥15%↓	0.68	2.38	(0.78, 7.44)
(<1.67xULN & ≥15%↓) or (<2.0xULN & ≥40%↓)	0.69	2.68	(0.89, 7.21)

Subgroup Analyses

1. Age (<65 or ≥65)

2. Age at diagnosis (>45 or ≤45)

3. ALP baseline raw values (u/l)

   (≤277.5; >277.5 and ≤465.5; >465.5)

4. Region (Europe vs. North America)

5. Year of diagnosis (<1990 and 1990-2009)

Three Cutoffs have Similar Analysis Results
(except Age and Diagnosis year<1990)
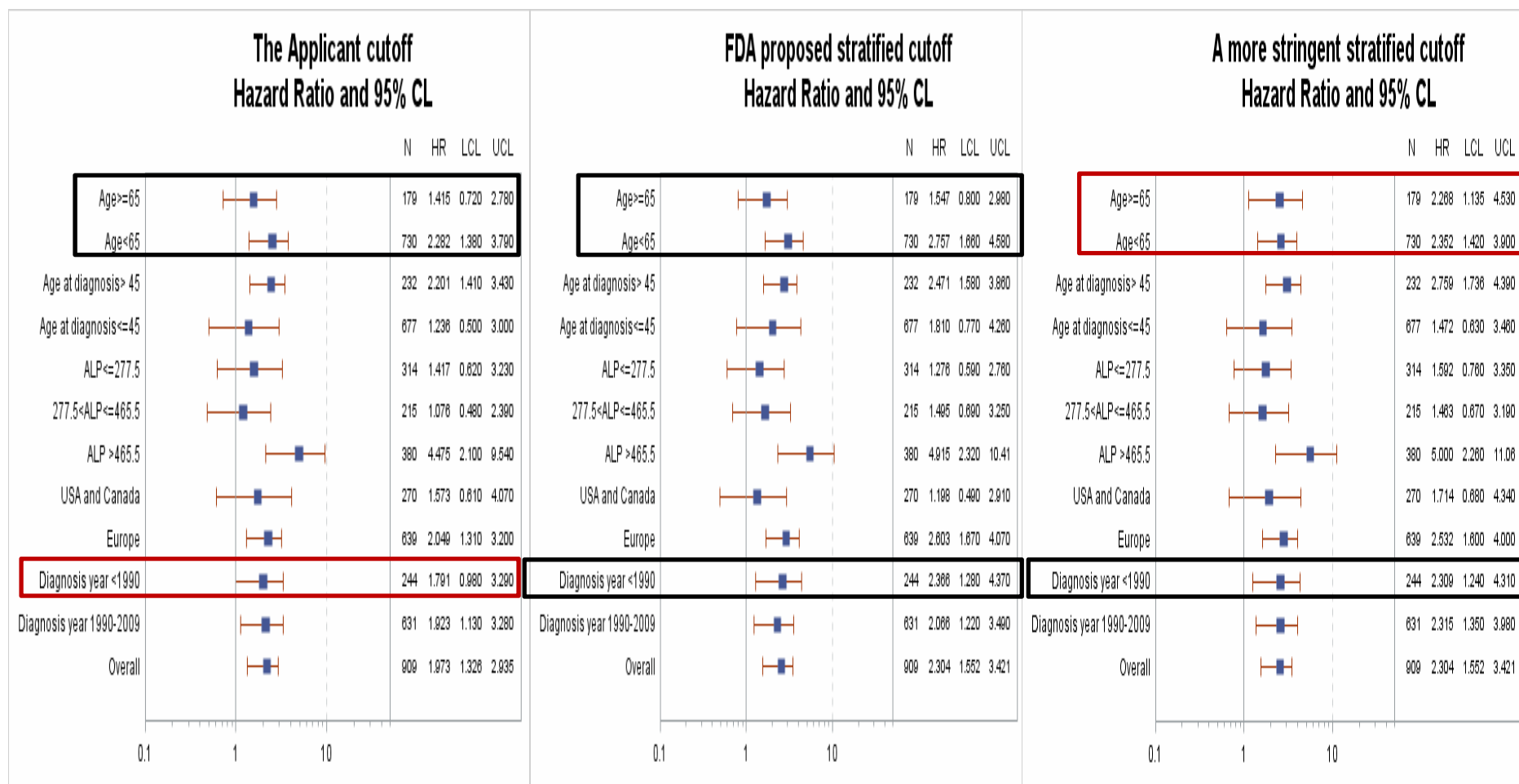
The FDA Proposed Stratified Cutoff Demonstrates Wider Separation Between Kaplan-Meier Curves

The Applicant's Cutoff

The FDA Proposed Stratified Cutoff
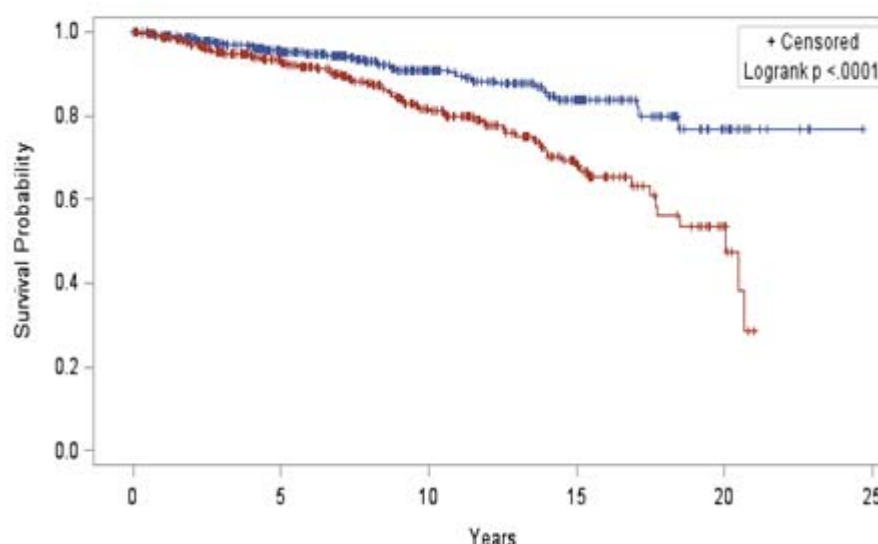
Limitations

- Only the "years" of all the important variables were provided such as "date of diagnosis of PBC", "UDCA date of start therapy",…etc.

- Region information was only categorized as USA, Canada and Europe, not as countries or centers.

- The Global PBC database was composed of observational and retrospective registry data. There is a large amount of missing information/data.

Summary of Findings

- The model with the factors of age, baseline ALP raw lab values, and PGALP12 was chosen for the model to predict death or liver transplant in the study population

- The FDA proposed stratified cutoff results in similar point estimates of C-statistic compared to other combined or stratified cutoffs (i.e., 0.68 to 0.69 in the training sets and 0.68 to 0.70 in the testing sets, respectively)

Summary of Findings

- The FDA proposed stratified cutoff (<2.0xULN & ≥40%↓; <1.67xULN & ≥15%↓) has demonstrated numerically better performance than the Applicant's cutoff.

- Subgroup analysis results demonstrate that the estimated hazard ratios of association between the cutoffs and the clinical outcome appears to be consistent, although some of their 95% confidence intervals are narrower or wider.

Outline

- Obeticholic Acid: General Aspects
- Clinical Development Program
- Efficacy:
  - Phase 2
  - Phase 3
  - Monotherapy
- Safety
  - Hepatic adverse events
  - HDLc reduction

Outline

- **Obeticholic Acid: General Aspects**
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Primary Biliary Cholangitis/Cirrhosis (PBC)

- PBC is a rare, and a slowly progressive (over decades), cholestatic liver disease
- Female to male ratio is ~10:1, mean age of diagnosis is 40-60 years of age
- About 40% of PBC patients achieve partial biochemical response (as assessed by the responder criteria) with ursodeoxycholic acid (UDCA), which is the only FDA approved treatment for PBC

Biochemical Responder Criteria

Criteria	Definition of the biochemical response
Mayo 1999	Alkaline Phosphatase (ALP) <2 XULN
Barcelona 2006	> 40% decrease in ALP or normalization
Paris-1 2008	ALP < 3.0xULN, AST < 2.0xULN and total bilirubin (TB) ≤ 1mg/dL
Rotterdam 2006	Normalization of abnormal bilirubin and/or albumin
Toronto 2010	**ALP ≤ 1.67xULN**
Paris-2 2011	ALP ≤ 1.5xULN, AST ≤ 1.5xULN and bilirubin ≤ 1mg/dL
Mayo 2011	**ALP ≤ 1.67xULN and total bilirubin ≤ 1mg/dL (ULN)**

OCA

- Proposed Indication:
    - Treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA

- Proposed Dosing Regimen:
    - 5 mg for 3 months and up-titrate based on tolerability, and biochemical response to 10 mg

- OCA is not marketed in the U.S. or any other country

Outline

- Obeticholic Acid: General Aspects
- **Clinical Development Program**
- Efficacy:
  - Phase 2
  - Phase 3
  - Monotherapy
- Safety
  - Hepatic adverse events
  - Reduction in HDL

Phase 2 and 3 Clinical Program

- Phase 2
  - 747-201: OCA monotherapy (3 months)
  - 747-202: OCA + UDCA (3 months)

- Phase 3 (Pivotal)
  - 747-301: OCA ± UDCA (12 months)

Overview of the Phase 2 and 3 Clinical Program

Study	747-201	747-202	747-301
Total Number of Patients (n)	59	138	216
Treatment	Placebo 10 mg 50 mg	Placebo 10 mg 25 mg 50 mg	Placebo 5mg 10 mg
Patient Inclusion Criteria	ALP between 1.5xULN and 10xULN		ALP≥1.67xULN and/or 1.0×ULN <TB < 2.0×ULN
Primary Endpoint	Percent change in ALP from baseline to month 3		ALP <1.67 x ULN and ≥15% reduction in ALP and, TB ≤ULN at month 12

Stages of Disease (Rotterdam Criteria)*

- **Early:**
  - Elevated ALP, normal TB, normal albumin

- **Moderately advanced:**
  - Either low albumin or high TB

- **Advanced:**
  - Both low albumin + high TB

*Kuiper EM, Gastroenterology. 2009 Apr;136(4):1281-7

Stages of Disease for PBC Patients in the OCA Clinical Program

Rotterdam Criteria	747-201 n(%)	747-202	747-301
Early	46(78%)	137 (83%)	195 (90%)
Moderately advanced	13 (22%)	25 (15%)	21 (10%)
Advanced	0	3 (2%)	0

Reference range for this slide only:
Alkaline Phosphatase (ALP) ULN: 118.3 U/L (females), 124.2 U/L (males);
Total Bilirubin (TB) ULN: 19.32 µmol/L (females), 25.48 µmol/L (males);
Albumin LLN: 35 g/L (females and males)

Patient Disposition and Stage of Disease
Trial 747-201

	Placebo	OCA 10 mg	OCA 50 mg
Patients Enrolled - n	23	20	16
Patients Completed - n (%)	23 (100%)	16 (80%)	9 (56%)

Rotterdam Criteria	Placebo (N=23) n (%)	OCA 10 mg (N=20) n (%)	OCA 50 mg (N=16) n (%)	Total (N=59) n (%)
Early	20 (87%)	11 (55%)	15 (94%)	46(78)
Moderately advanced	3	9 (45%)	1(6%)	13(22)
Advanced	0	0	0	0

Absolute Change from Baseline to End of Treatment in Mean ALP Over Time
Trial 747-201
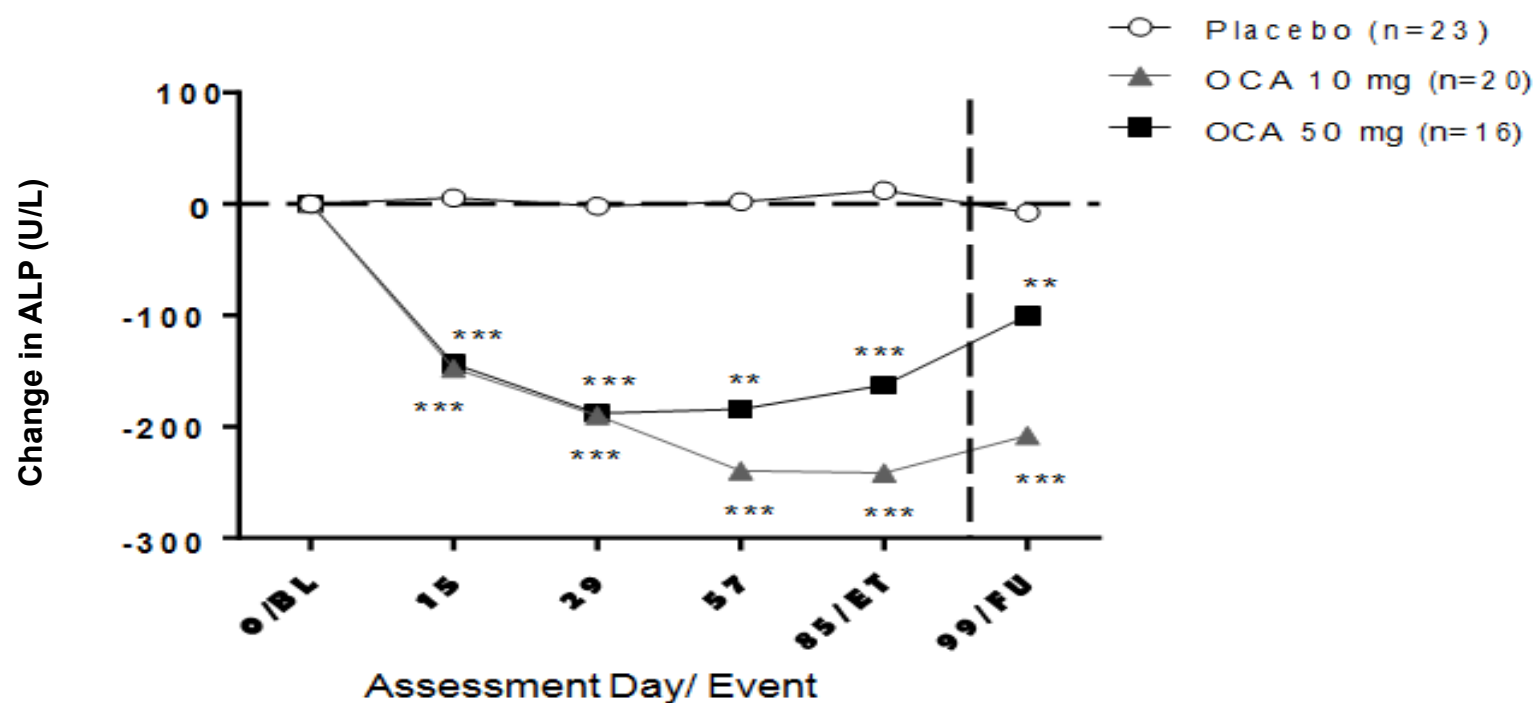
Source: Applicant's NDA Submission

Primary Efficacy Analysis: ALP Percent Change
Trial 747-201

	Placebo (n = 23)	OCA 10 mg (n = 20)	OCA 50 mg (n = 16)
Mean (SD)	0.4 (15.3)	-44.5 (24.4)	-37.6 (21.0)
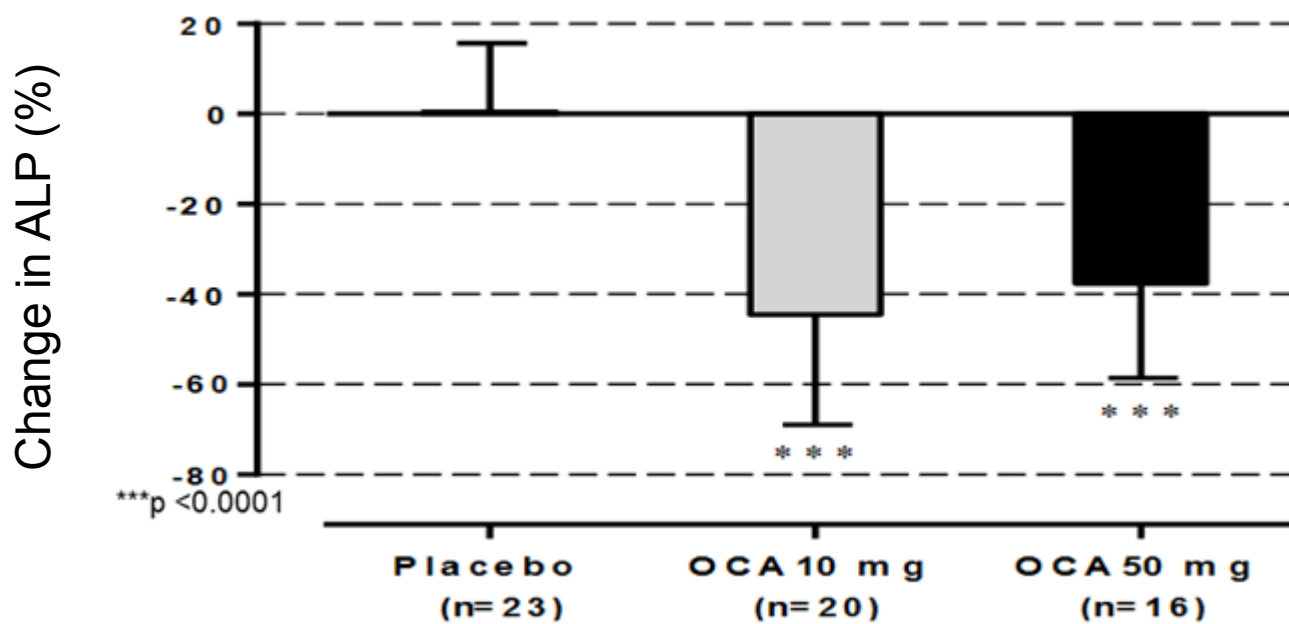
***p <0.0001

Trial 747-202
OCA + UDCA

Stages of Disease
Trial 747-202

Rotterdam Criteria	Placebo N=38	OCA 10 mg N=38	OCA 25 mg N=48	OCA 50 mg N=41
Early	35 (92%)	29 (76%)	39 (81%)	34 (83%)
Moderately advanced	3 (8%)	8 (21%)	7 (15%)	7 (17%)
Advanced	0	1 (3%)	2 (4%)	0

Mean ALP Over Time
Trial 747-202
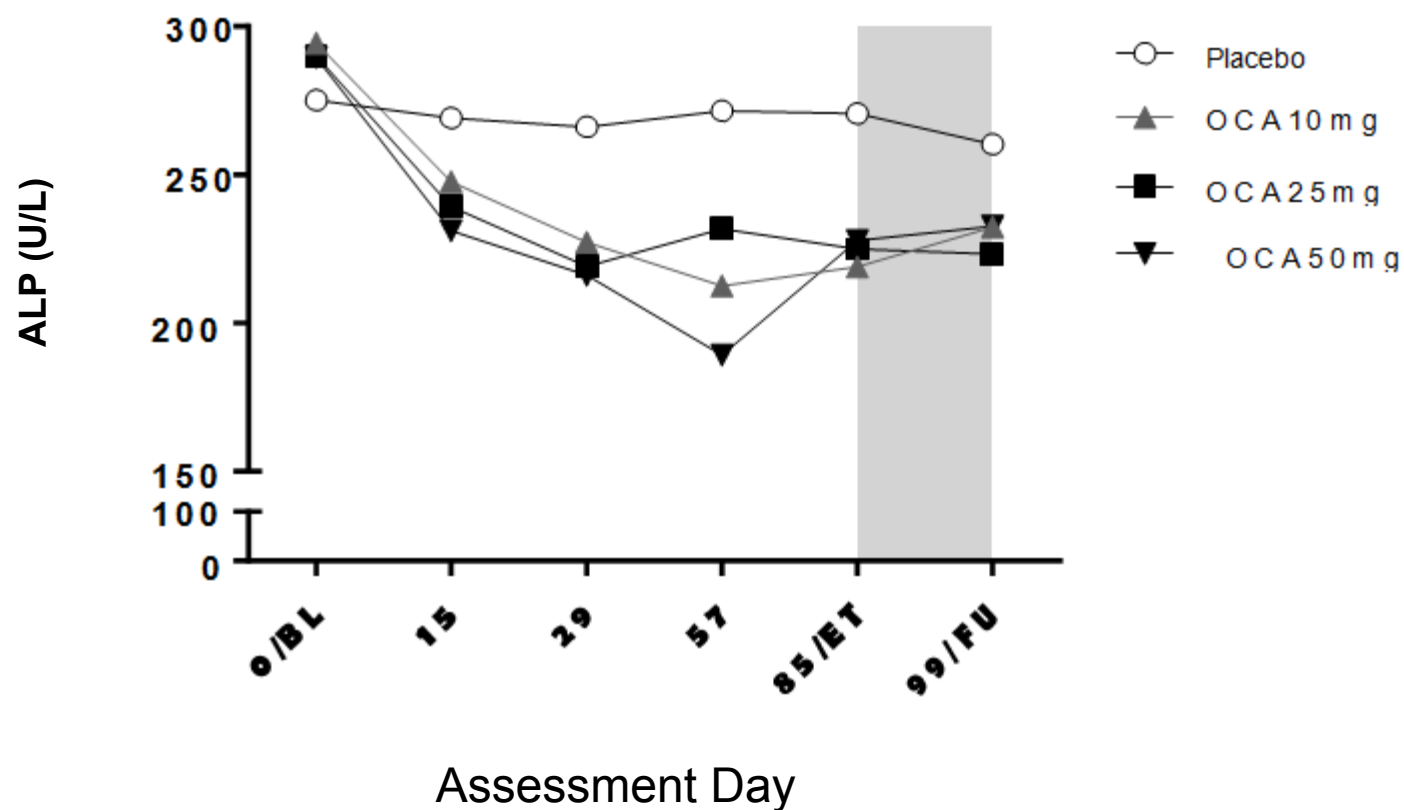
Source: Applicant's NDA Submission

Primary Efficacy Analysis:
ALP Percent Change Trial 747-202

	Placebo (n = 37)	OCA 10 mg (n = 38)	OCA 25 mg (n = 47)	OCA 50 mg (n = 39)
Mean (SD)	-2.6 (12.5)	-23.7 (17.8)	-24.7 (17.9)	-21.0 (27.6)
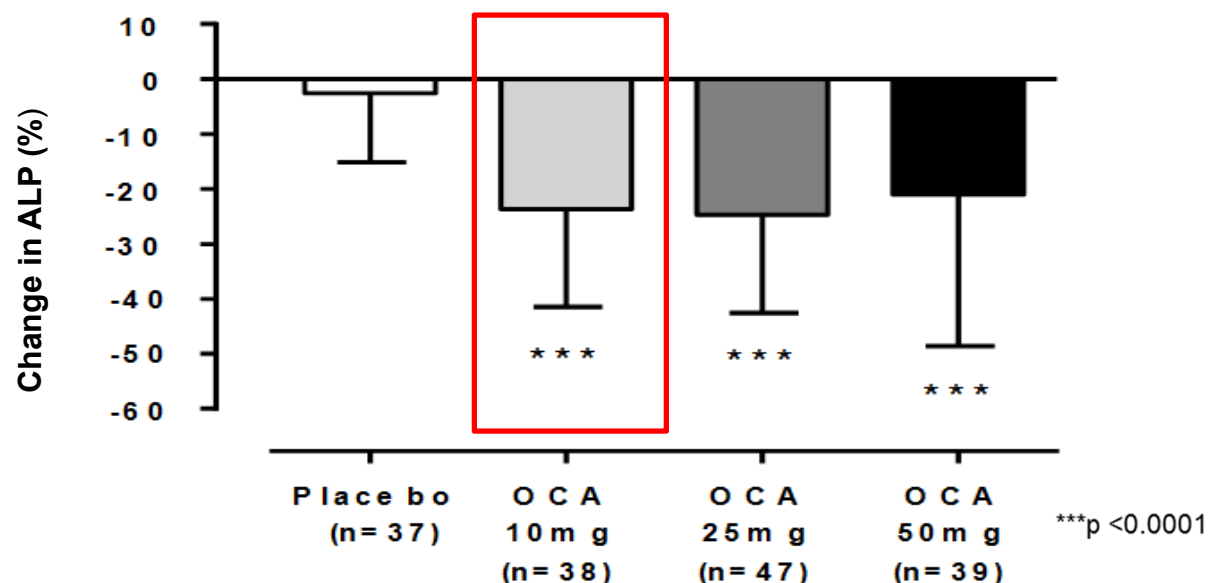
Source: Applicant's NDA Submission

Trial 747-301

Phase 3 Pivotal Trial

OCA ± UDCA

Primary Efficacy Endpoint
Trial 747-301

The primary efficacy endpoint* was achieving:

- Serum ALP <1.67 X ULN **AND**

- Decrease in ALP of ≥15% **AND**

- TB ≤ ULN

Three arm trial (12 months):

Placebo

OCA Titration arm (5 mg titrated to 10 mg)

OCA 10 mg

Section 7.1.1 -page 63 of 391-Protocol 747-301 Amendment 3, dated 24 September 2012- Primary efficacy endpoint agreed upon and as submitted to FDA in the latest amendment)

Stages of Disease
Trial 747-301

Rotterdam Criteria	Placebo (N = 73) n (%)	OCA Titration (N = 70) n (%)	OCA 10 mg (N = 73) n (%)
Early	65 (89%)	64 (91%)	66 (90%)
Moderately advanced	8 (11%)	6 (9%)	7 (10%)
Advanced	0	0	0

Patient Disposition
Trial 747-301

Patients	Placebo	OCA Titration	OCA 10 mg	Total
Dosed	73	70	73	216
Completed 12 months	70 (96%)	64 (90%)	64 (88%)	198 (91%)
Primary Reason for Discontinuation from 12-month Double-Blind Phase n (%)				
Death	0	1 (1)	0	1 (<1)
Pruritus	0	1 (1)	7(10)	8 (4)

Mean ALP Values Over Time
Trial 747-301

Mean (SD) ALP Values Over Time and LTSE
Trial 747-301
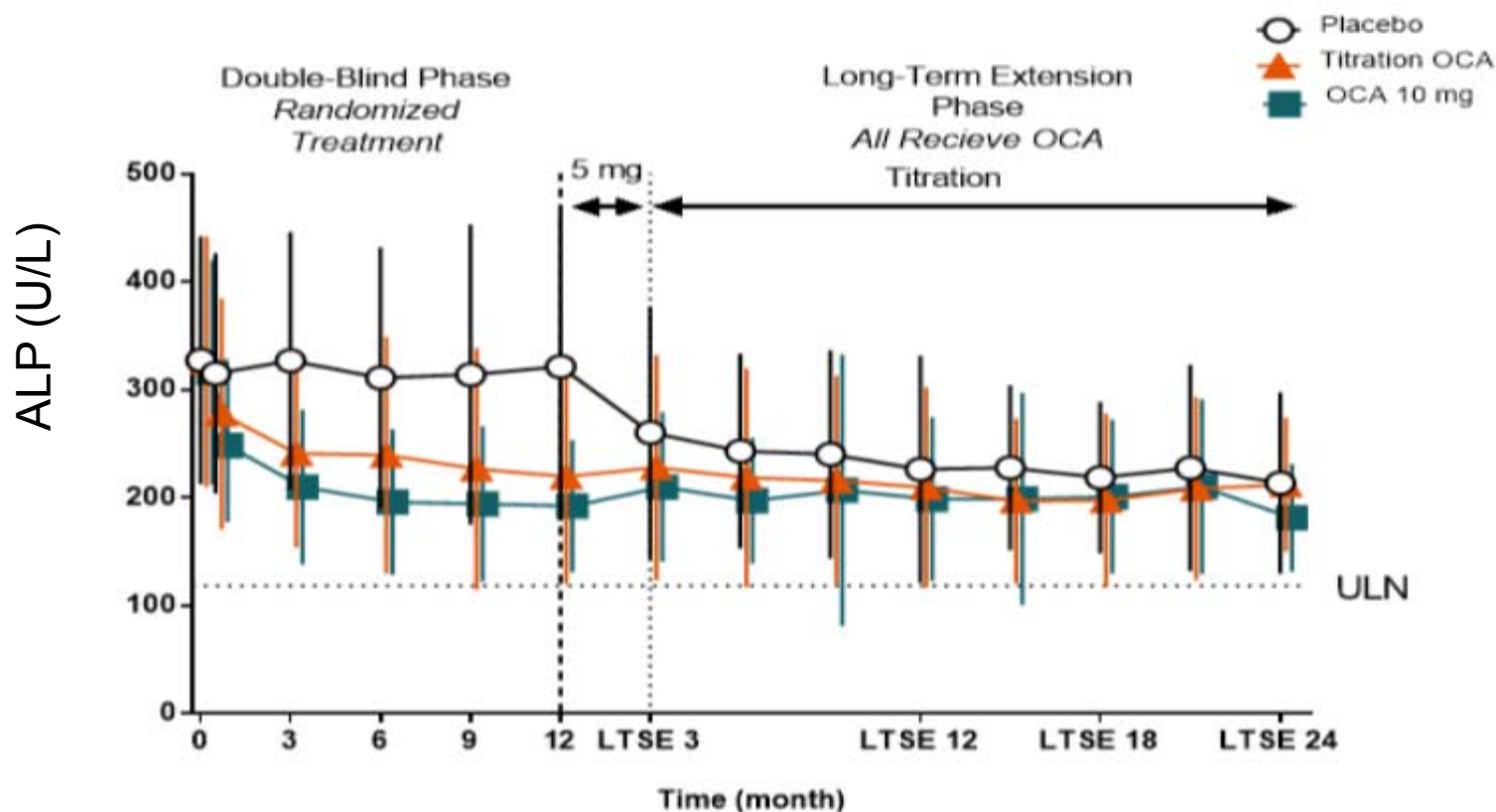
Source: Applicant's NDA Submission

Components of the
Primary Composite Endpoints
Trial 747-301

Criterion	OCA 10 mg N=73 n (%)	OCA titration N=70 n (%)	Placebo N=73 n (%)
ALP ≤ 1.67×ULN at Month 12	40 (54.8%)	33 (47.1%)	12 (16.4%)
Decrease in ALP ≥ 15% at Month 12	57 (78.1%)	54 (77.1%)	21 (28.8%)
TB ≤ 1.0×ULN at Month 12	60 (82.2%)	62 (88.6%)	57 (78.1%)

Total Bilirubin
Trial 747-301

	OCA10 mg (N = 73)	OCA Titration (N = 70)	Placebo (N = 73)
Baseline TB Concentration			
TB ≤ 1.0 X ULN	66 (90.4%)	66 (94.3%)	66 (90.4%)
1.0×ULN < TB < 2.0×ULN	7 (9.6%)	4 (5.7%)	6 (8.2%)
TB ≥ 2.0×ULN	0	0	1 (1.4%)
Baseline TB Concentration (X ULN)			
Mean (standard deviation)	0.55 (0.31)	0.51 (0.24)	0.60 (0.37)
Median	0.47	0.45	0.48
Min, Max	0.08, 1.78	0.11, 1.43	0.12, 2.03

Source: FDA Reviewer's Table generated from ADLIVER dataset

Subset of Patients with Elevated Total Bilirubin at Baseline Trial 747-301

	10 mg OCA N=73	OCA Titration N=70	Placebo N=73
TB > 1.0×ULN at Baseline	7 (10%)	4 (6%)	7 (10%)
TB ≤1.0×ULN at Month 12	5	2	1
Achieved Primary Composite Endpoint at Month 12	2	1	0

Source: FDA Reviewer's Table generated from ADLIVER dataset.

Variability in Total Bilirubin
Trial 747-301

- Trial 301 was not designed to show efficacy with respect to reduction of TB within normal reference range

- TB remained within normal reference range in majority of patients for the duration of trial across all treatment arm, not just OCA treated arm

- The significance of small decremental changes in TB that remain within the normal reference range over a 12 month duration is unknown

- Extent of variability in TB over time in PBC is unknown; changes in TB during treatment trials must be considered in the context of background changes of TB. As exemplified in trial 747-301:

  - 22 patients had high TB at screening,
  - 15 patients had high TB on repeat measure within 8 weeks (i.e. Day 0)
  - Average of the two values (Screening +Day 0) led to a total of 18 patients with high TB.

Mean (SD) Total Bilirubin and LTSE
Trial 747-301
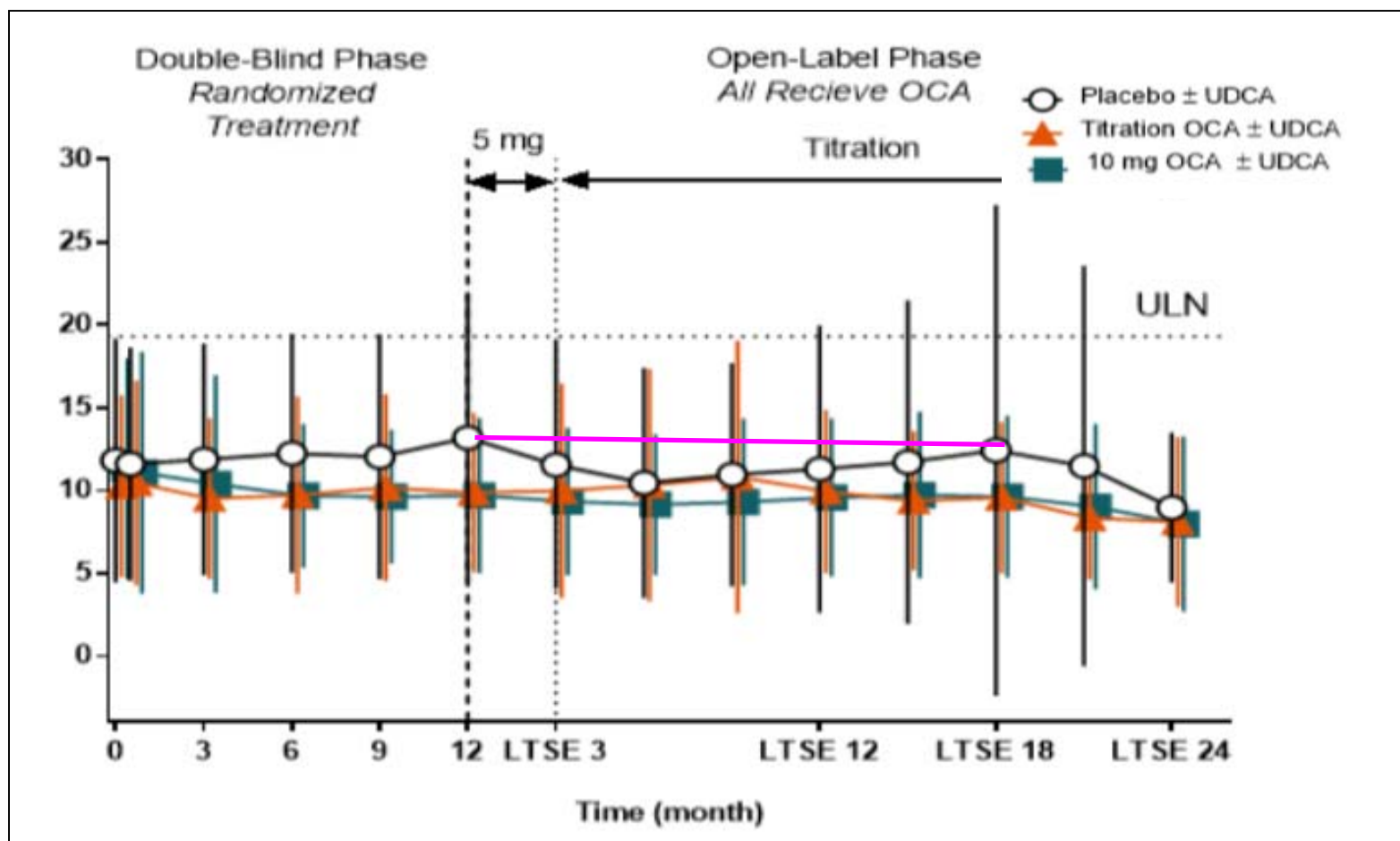
Re-analyses with FDA Stratified ALP Cutoffs
Trial 747-301

- If baseline ALP was ≥ 2.0×ULN, then a patient was designated as a responder if both of the following criteria were met:

  – Month 12 value of ALP < 2.0×ULN

  – ALP reduction from baseline at Month 12 ≥ 40%;

- If baseline ALP was ≥ 1.67×ULN but < 2.0×ULN, the patient was designated as a responder if both of the following criteria were met:

  – Month 12 value of ALP < 1.67×ULN

  – ALP reduction from baseline at Month 12 ≥ 15%.

Proportion of Patients who Achieved Response at Month 12
Trial 747-301

	OCA 10 mg N=60 n (%)	OCA titration N=60 n (%)	Placebo N=61 n (%)
Threshold Proposed by Intercept			
ALP < 1.67×ULN and Decrease ≥ 15%	35 (58.3%)	28 (46.7%)	7 (11.5%)
Threshold Proposed by FDA			
ALP < 2.0×ULN and Decrease ≥ 40% AND ALP < 2.0×ULN and Decrease ≥ 15% (Nominal p-value)	26 (43.3%) (<0.0001)	23 (38.3%) (<0.0001)	3 (4.9%)

Source: Reviewer's Table generated from ADLIVER dataset

Efficacy Conclusions
Trial 747-301

Relative to placebo, a statistically significant proportion of patients in the OCA 10 mg arm and OCA titration arm achieved ALP reductions

OCA as Monotherapy
Trials 747-201, 747-202 and 747-301

Responders at Month 3: Pooled data from Phase 2 and 3

	Applicant's Composite Endpoint: ALP <1.67x ULN and Total Bilirubin ≤ULN, and ALP Decrease of ≥15% from Baseline
	Responders at Month 3
Monotherapy	
Placebo (N = 28)	1 (4%)
OCA 10 mg (N = 26)	10 (38%)
Combination (+ UDCA)	
Placebo (N = 106)	5 (5%)
OCA 10 mg (N = 105)	43 (41%)

Reductions in ALP Biomarker with Monotherapy Pooled Data: Trials 747-201, 747-202 and 747-301

Monotherapy Vs. Combination with UDCA

LS Mean ALP (U/L) Values at Baseline and Month 3
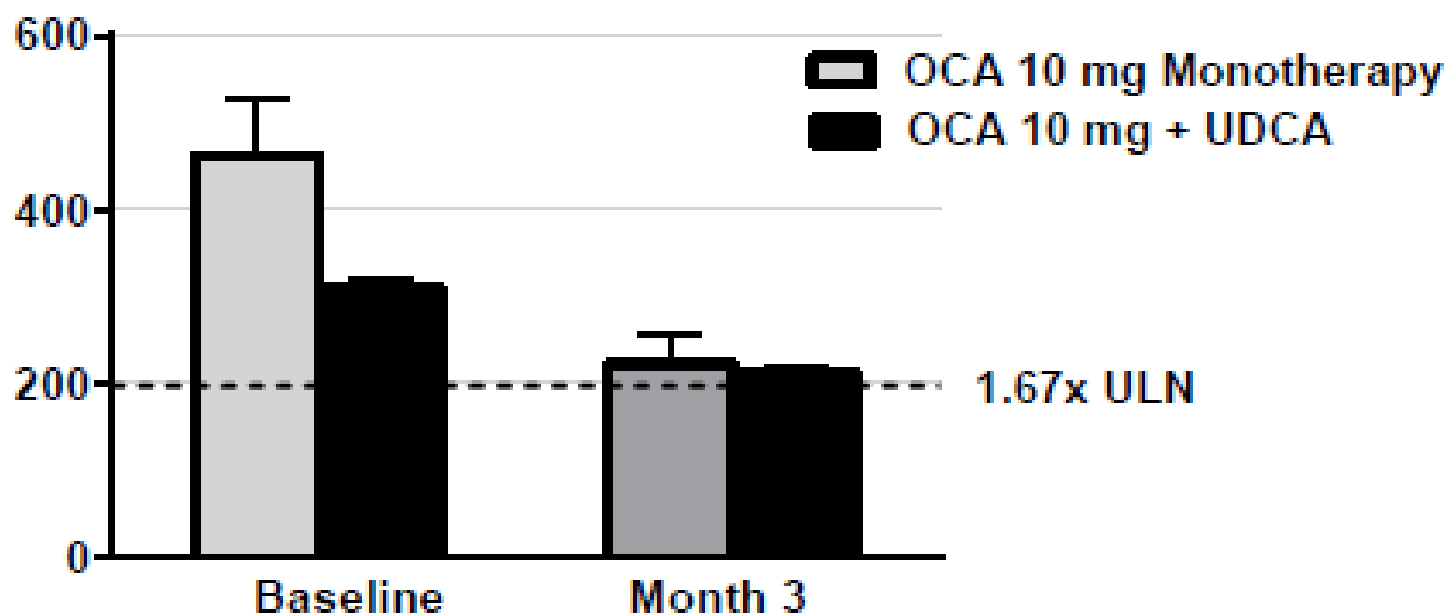
Source: Applicant's NDA Submission

Reductions in ALP Biomarker with Monotherapy Pooled Data: Trials 747-201, 747-202 and 747-301

Monotherapy Vs. Combination therapy

Source: Applicant's NDA Submission

Safety Summary

- Adverse events (AEs)
- Hepatic AEs
- HDLc reduction

Summary of Adverse Events
Trial 747-301

Adverse Reaction	OCA±UDCA		Placebo±UDCA (N = 73)
	OCA Titration (N = 70)	OCA 10 mg (N = 73)	
Pruritus	56%	70%	38%
Fatigue	19%	25%	15%
Abdominal pain and Discomfort	19%	10%	14%
Rash	7%	10%	8%
Arthralgia	6%	10%	4%
Oropharyngeal pain	7%	8%	1%
Cough	6%	8%	7%
Dizziness	7%	7%	5%
Constipation	7%	7%	5%
Edema peripheral	3%	7%	3%
Palpitations	3%	7%	1%
Pyrexia	0%	7%	1%
Thyroid function abnormality	6%	4%	3%
Eczema	6%	3%	0%
Procedural pain	6%	1%	1%

Source: Applicant's NDA Submission

Hepatic Adverse Events

- The hepatic AEs that occurred during the trial were treatment emergent AEs (TEAE)

- No patient in the placebo group experienced hepatic AEs in trial 747-202 compared to 9 patients on OCA 50 mg dose who experienced hepatic TEAEs including biochemical changes or hepatic decompensation events

  – 3 of the 9 patients had decompensation events (new onset jaundice, PBC flare, ascites and gastro-esophageal bleeding)

Integrated Summary of Hepatic Adverse Events

Exposure Adjusted Incidence- 100 persons exposure years (PEY)					
Placebo (N=134, PEY=84)	Titration (N=70, PEY=67)	10 mg (N=131, PEY=76)	25 mg (N=48, PEY=10)	50 mg (N=57, PEY=9)	Total OCA (N=306, PEY=163)
2.4	4.5	5.2	19.8	54.5	8.6

Placebo: non-serious liver function test abnormality in one patient; and esophageal variceal bleeding (serious) in 2nd patient

OCA 10 mg arm and titration: Ascites requiring paracentesis, esophageal variceal bleeding, jaundice, hepatic encephalopathy and changes in liver biochemistries (ALT/AST increase, bilirubin increase, and increase of INR)

OCA 25 mg and 50 mg groups: Serious AEs were: new onset ascites, primary biliary cirrhosis flare, jaundice, portal hypertension; The non-serious AEs were: alanine aminotransferase increased, aspartate aminotransferase increased, and bilirubin conjugated increased.

Source: Applicant's NDA Submission

Safety

- Adverse events (AEs)

- Hepatic AEs

- HDLc reduction

Changes in Mean HDL Cholesterol
Trial 747-201

	OCA 10 mg N=20	OCA 50 mg N=16	Placebo N=23
Mean HDLc (mg/dL)			
Baseline	66.8	75.4	71
Day 85	52.5	59.9	70.7
Change at month 3	-14	-16	-0.3

Changes in Mean HDL Cholesterol
Trial 747-202

	OCA 10 mg (N = 38)	OCA 25 mg (N = 48)	OCA 50 mg (N = 41)	Placebo (N = 38)
Mean HDLc (mg/dL)				
Baseline	67.6	71.5	75.4	69.9
Day 85	58	61.4	58	73.7
Change at month 3	-10	-10	-17	+4

Changes in Mean HDL Cholesterol
Trial 747-301

	OCA 10 mg N=73	OCA titration N=70	Placebo N=73
Mean HDLc (mg/dL)			
Baseline	81.2	81.2	69.6
Month 12	61.8	69	69.6
Mean Change at month 12	-19.4	-12.2	0

HDLc Reductions
Trial 747-301

Patients with HDLc ≥ 2 SD reduction (44 mg/dL)	
Placebo	0
OCA titration	4
OCA 10 mg	5
Patients with HDLc ≥1 SD but ≤2 SD reduction (between 22 to 44 mg/dL)	
Placebo	1
OCA titration	14
OCA 10 mg	16

HDLc Reduction Outliers
Trial 747-301

Baseline HDLc (mg/dL)	Month 12 or end of treatment HDLc (mg/dL)	Decrease in HDLc (Month 12-Baseline) (mg/dL)
OCA 10 mg		
119.5	34	-85.5
112.1	34	-78.1
95.1	35.9	-59.2
75	29	-46
75	37	-38
40.9	8.1	-32.8
62.2	32.8	-29.4
35.1	6.9	-28.2
42.2	25.9	-16.3

HDLc Reduction Outliers
Trial 747-301

Baseline HDLc (mg/dL)	Month 12 or end of treatment HDLc (mg/dL)	Decrease in HDLc (Month 12-Baseline) (mg/dL)
OCA titration arm		
75	22	-53
68.5	22	-46
90.5	50	-40.5
64	38	-26
49.5	31	-18.5
56	37.8	-18.2

HDLc Reduction Outliers
Trial 747-301

Baseline HDLc (mg/dL)	Month 12 or end of treatment HDLc (mg/dL)	Decrease in HDLc (Month 12-Baseline) (mg/dL)
Placebo (Largest HDLc Reductions)		
93.5	54	-39.5
75.5	58	-17.5
83*	47	-36
128*	107	-21

*These patients received OCA instead of placebo

Lipid Assessment Trial
747-205

- A dedicated lipid assessment open label trial, utilizing OCA 10 mg dose was conducted:
  - Lipid modifying agents were prohibited
  - Treatment duration was 8 weeks with a follow up at week 12 (i.e., 4 weeks after OCA discontinuation)

Changes in Mean Serum HDLc

	Baseline (N=26)	Week 8/end of treatment (N=26)
HDLc (mg/dL)	75.38	57.81

Changes in HDL Cholesterol (mmol/L)
Trial 747-205
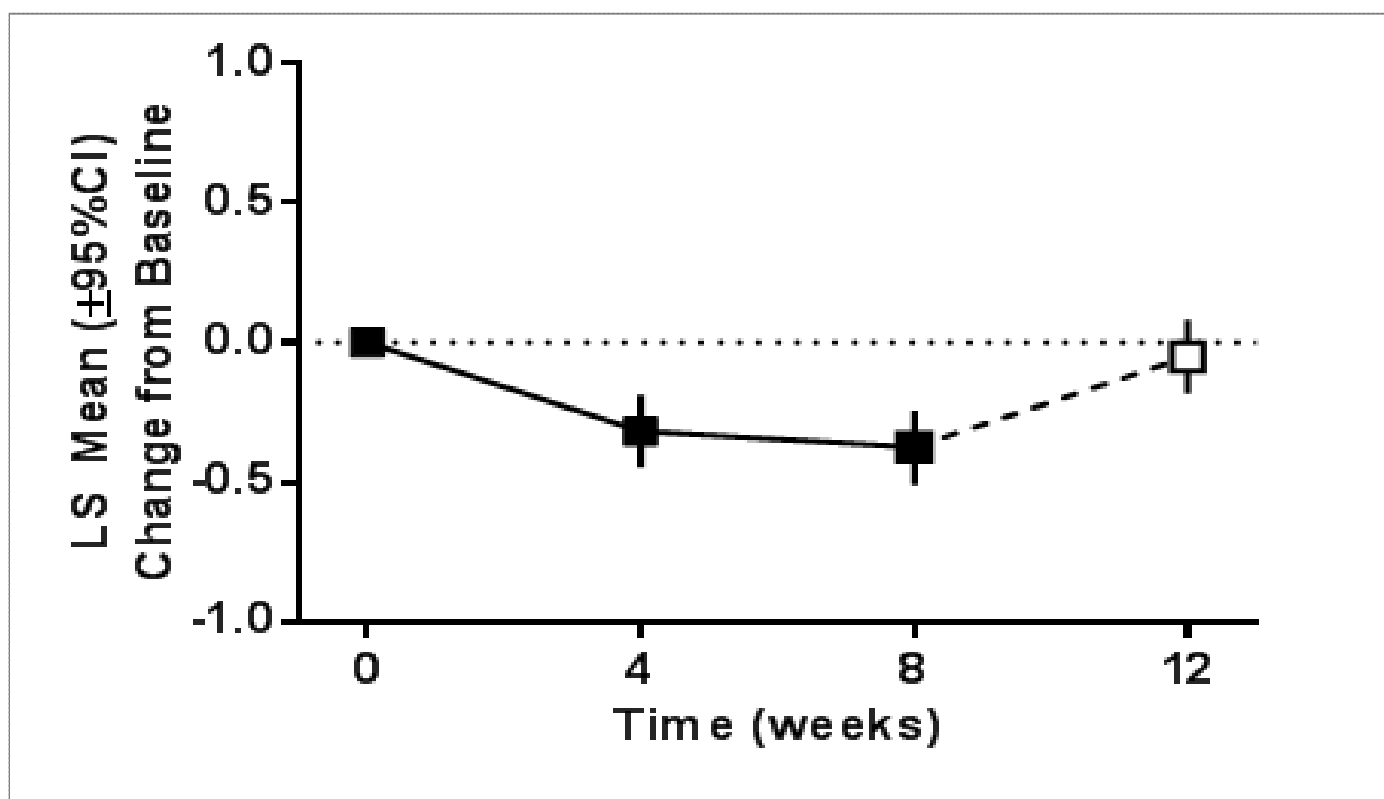
Source: Applicant's NDA Submission

Conclusions: HDLc Reduction

- HDLc reductions were noted across all PBC trials

  - Majority of patients experienced some degree of HDLc reductions

  - Some experienced reductions in HDLc levels ≥2 SD

  - HDLc in some patients declined from WNL to below LLN and the reductions were quite significant

- Even though there were a few patients on concomitant medications that might have altered the lipid profile, the lipid changes were consistent across all four trials in PBC patients

- There was a dose dependent trend in HDLc reduction

Conclusions: Hepatic AEs

- OCA doses higher than 10 mg may lead to higher rate of hepatic AE's

Overall Efficacy and Safety

- Additional long term safety data are needed:
  - In patients with moderately advanced and advanced stage disease
  - For use as monotherapy, in patients who are intolerant to UDCA
  - Patients who develop HDLc reduction

Dosing Considerations for Obeticholic Acid (OCA) for Primary Biliary Cirrhosis (PBC)

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April 7, 2016

A Starting Dose of 5 mg QD is Appropriate

- Phase 3 studied two different starting doses:
  - 5 mg QD and 10 mg QD

- Dose-dependent increase in pruritus related discontinuations:
  - placebo 0% (0/73), OCA 5 mg 1% (1/70), OCA 10 mg 10% (7/73)

- Better tolerability profile with time with a lower starting dose
  - less discontinuations,
  - less days of severe pruritus (9.1 vs. 31.4 days per subject-year),
  - delayed time to first onset of pruritus (24 vs. 9 days as median time)

- Similar efficacy at 1 year for titration arm with 5 mg starting dose and 10 mg arm (46% vs. 47% responders)

ALP Response Justifies Titration at 3 Months

- Phase 3 study: Patients up-titrated to 10 mg at 6 months
- Proposal: Initiate up-titration at an earlier time (i.e. 3 months)
- Rationale: Reduction in ALP plateaus at 3 months with 5 mg QD
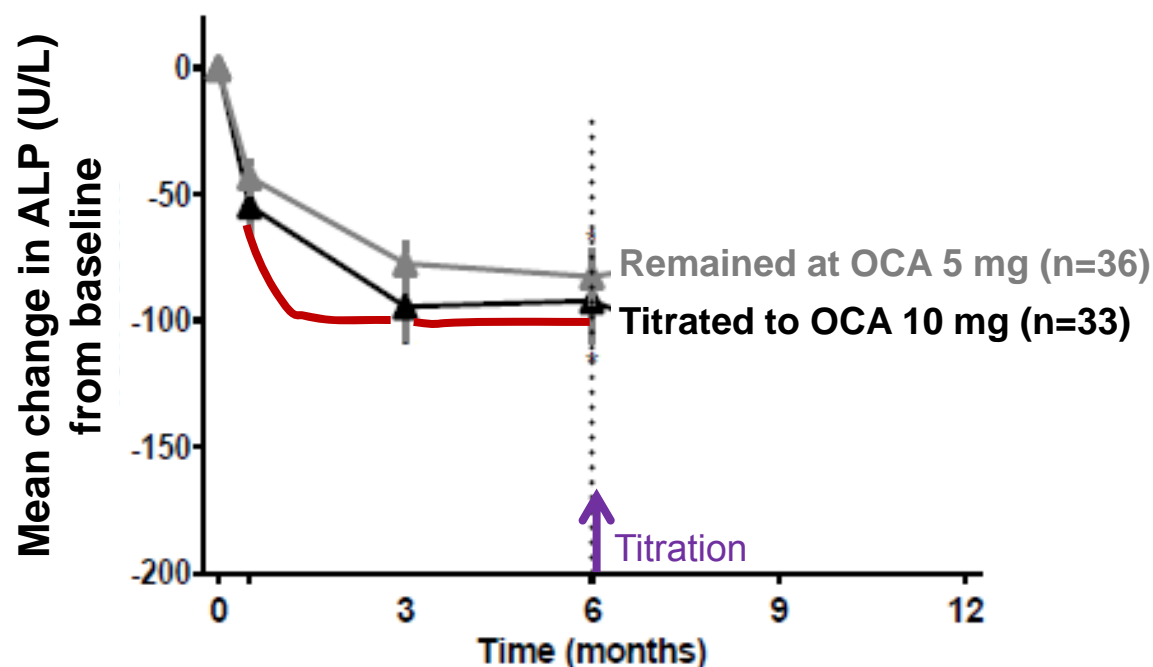
- Data collected only at week 2 and at month 3, plateau could be earlier than 3 months. Up-titration at a time earlier than 3 months?

Time Profile of Safety Events Justifies Titration at 3 Months

- Almost all (7 of 8) of the discontinuations due to pruritus occurred over the first 3 month period with OCA treatment in phase 3; rarely any after 3 months.

- Thus, a minimum duration of 3 months will give fair idea of tolerability of starting dose and identification of subjects with tolerability for further up-titration.

Titration to 10 mg is an Important Component Towards Efficacy

- On a mean level, more time on 5 mg QD does not achieve better ALP response

- Titration to 10 mg QD achieves better response (further ALP reduction)
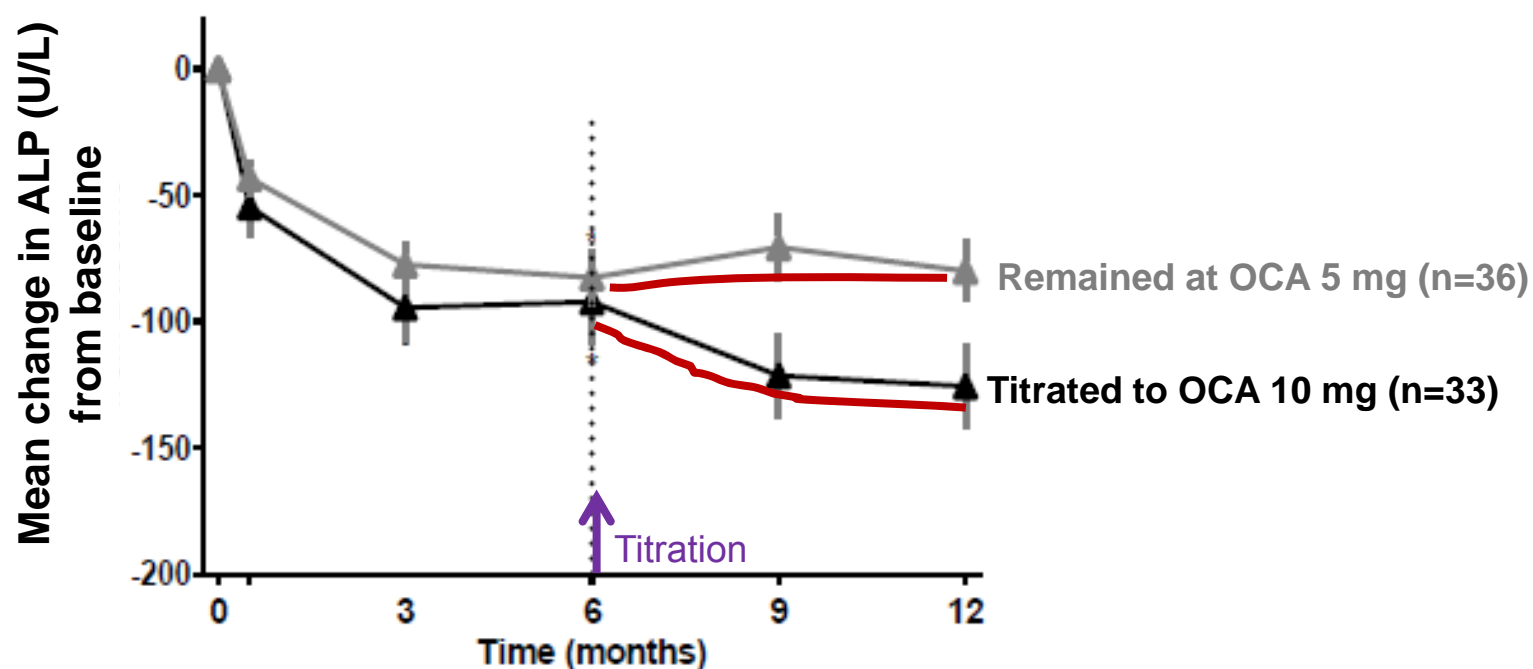
Titration to 10 mg is an Important Component Towards Efficacy

Treatment	Achievement of Primary Endpoint at 6M / 12M			
	- / -	- / +	+ / -	+ / +
Titration Arm (N=70)				
5 mg (N=37)	11 (29.7%)	2 (5.4%)	7 (18.9%)	17 (45.9%)
5 mg→10 mg (N=33)	20 (60.6%)	13 (39.4%)	*	*
10 mg (N=73)	32 (43.8%)	4 (5.5%)	7 (9.6%)	30 (41.1%)
Placebo (N=73)	66 (90.4%)	2 (2.7%)	0 (0%)	5 (6.9%)

Not Applicable

- 5 mg→10 mg: 13 additional responders from month 6 to month 12
- 5 mg: ~19% of responders at month 6 became non-responders by month 12. These may benefit from up-titration to 10 mg

Summary-1

- The proposed starting dose of 5 mg QD with titration to 10 mg QD after 3 months is appropriate for overall population

- Physicians should **continue to evaluate biochemical response** (reduction in ALP) **longitudinally** and **utilize the up-titration rule any time after 3 months** from treatment initiation

Agenda

- Appropriateness of the Applicant's proposed starting dose of 5 mg once daily (QD) with titration to 10 mg QD after 3 months for overall population

- **Dose adjustment for patients with moderate or severe hepatic impairment (HI)**

- Discontinuation of OCA for lack of biochemical response

Dosing for Hepatic Impairment (HI)

- A small single dose trial is conducted in healthy subjects (normal hepatic function) and subjects with hepatic impairment (Child-Pugh A/B/C).

    - changes in concentrations/clearance quantified

- Using pharmacokinetic (PK) principles, a dose/dosing regimen is derived that can achieve matching exposures to general patient population with normal hepatic function - typically plasma exposures

- PBC is a special case: site of efficacy and probable safety is the same as the site of drug biotransformation, which impacts clearance - quantification of anticipated changes in liver exposure would have value in addition to plasma exposure.

- A physiology based PK model was developed by the Applicant to characterize plasma exposure and predict liver exposure

    - useful to predict exposures with different doses/dosing regimens

Moderate/Severe HI Results in Higher Total OCA Plasma Exposures

- Total OCA = OCA + active conjugates (glyco-/tauro-OCA)

Study with 10 mg single dose
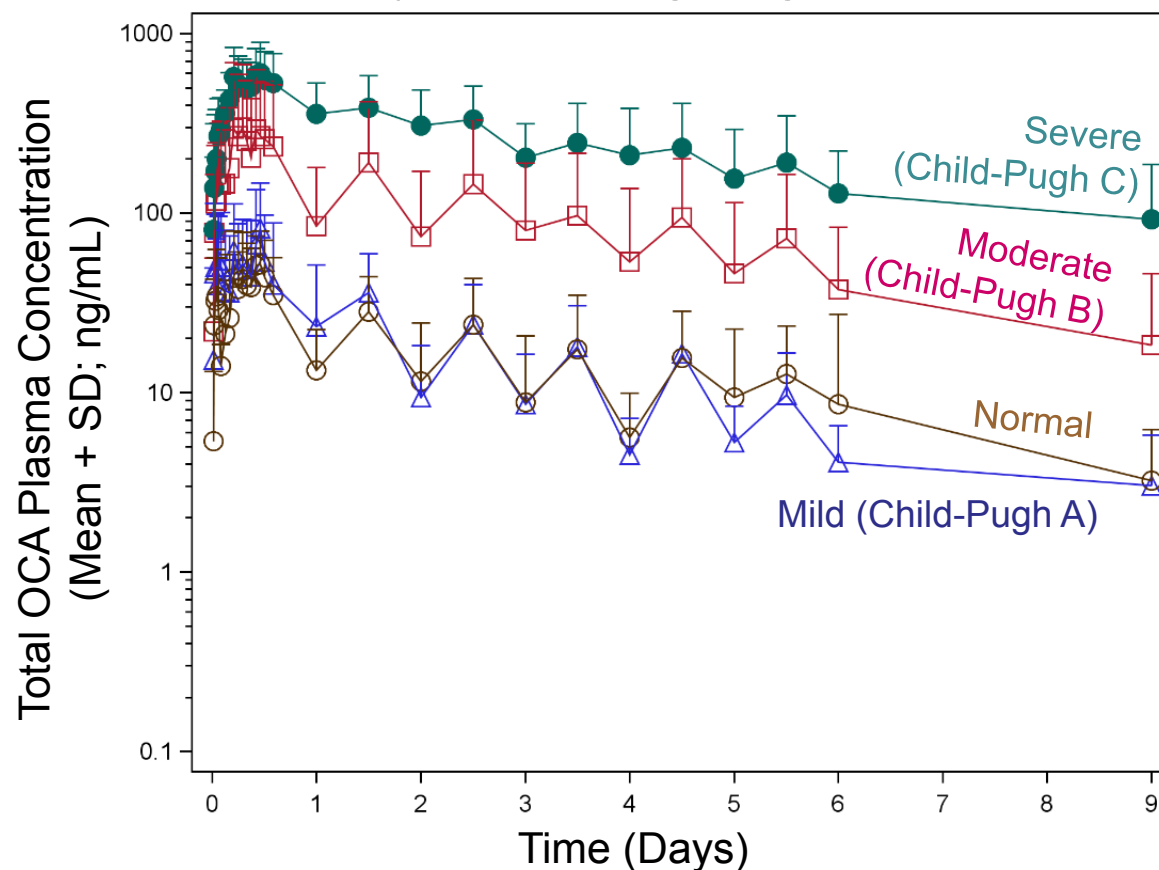
AUC$_{0-t}$ of total OCA (N=8)

Comparison vs. Normal	Fold-Change (90% CI)
Mild	**1.13** (0.6-2.3)
Moderate	**4.20** (2.1-8.4)
Severe	**17.30** (8.7-34.4)

Applicant's Physiology Based PK Model to Quantify Changes in Plasma & Liver Exposures of OCA/Conjugates

- Incorporates:
  - Oral input of OCA into gut
  - Systemic and hepatobiliary fluxes, flux to gall bladder and gut
  - Biotransformation (glyco-& tauro-OCA) of/to OCA in liver and gut
  - Meal induced gall-bladder emptying of drug/conjugates to gut
  - Clearance of OCA through gut
  - Change in biotransformation rate and flow shunting with hepatic impairment (HI)

- OCA specific biotransformation and transport rates were fitted using plasma PK of OCA, glyco- and tauro-OCA

~Two-fold Total OCA Liver Exposures Predicted in Subjects With Severe HI

Study with 10 mg single dose: AUC_{0-t} of **total OCA**

Comparison vs. Normal	Fold-Change (90% CI)		
	Plasma - observed*	Plasma - predicted**	Liver - predicted**
Mild	**1.13** (0.6-2.3)	1.35	1.12
Moderate	**4.20** (2.1-8.4)	**8.03**	**1.47**
Severe	**17.30** (8.7-34.4)	**13.2**	**1.74**

- Model reasonably describes exposures in different HI groups (specifically normal, mild/severe HI; some over-prediction for moderate HI)

- Applicant's initial proposal: No dose adjustment for any HI category
  - Dose adjustment may lead to lower liver exposures, might be suboptimal from efficacy perspective

FDA's Position: Dose Adjustment Desirable

Rationale: Efficacy/Safety

- No clear benefit of high exposures → Dose/Exposure-Response relationship for reduction in ALP plateaus at exposures for 10 mg QD

- Dose-response relationship for pruritus → higher discontinuations at higher exposures in PBC; hepatic AEs at higher exposures

Incidences of discontinuations due to pruritus

Trial (Duration)	Placebo	OCA (QD)			
		5 mg	10 mg	25 mg	50 mg
Phase 3 Study 301 (12 months)	0% (0/73)	1% (1/70)	10% (7/73)		
Phase 2 Study 202 (3 months)	0% (0/38)		8% (3/38)	8% (4/48)	24% (10/41)
Phase 2 Study 201 (3 months)	0% (0/23)		15% (3/20)		38% (6/16)

FDA's Position: Dose Adjustment Desirable

- Unknowns:
  - pruritus driven by plasma exposures or liver exposures?
  - impact of x-fold changes in liver exposures on pruritus?

- With same dose (5 mg QD), potential for high plasma/liver exposures → discontinuation and hepatic AE for patients with HI (Child-Pugh B / C)

- **Proposal: Initial dosing regimen in moderate/severe HI to match plasma exposures to normal (no or mild HI) PBC subjects**
  - likely avoid potential safety/discontinuation issues
  - allows identification of subjects for up-titration at ≥3 months

- **Further up-titration with dose/dosing regimen to meet efficacy goals**

Starting Dose of 5 mg Once Weekly (QW) in Moderate/Severe HI Achieves Similar Total OCA Plasma Exposures to 5 mg QD in Normal/Mild HI

Plasma and liver concentrations (every 24 hour) with different dosing regimen

Agenda

- Appropriateness of the Applicant's proposed starting dose of 5 mg once daily (QD) with titration to 10 mg QD after 3 months for overall population

- Dose adjustment for patients with moderate or severe hepatic impairment (HI)

- Discontinuation of OCA for lack of biochemical response
  - Consideration based on no/marginal ALP response
  - Time of discontinuation

Discontinuation of OCA for Lack of Biochemical Response

- No clear instructions for continuation or discontinuation of OCA for patients who have no or marginal reduction in ALP

- Currently, insufficient evidence of mechanism for long term efficacy of OCA in subjects who have no or marginal reduction in ALP

- Continuation of therapy should be weighed against the possible unfavorable lipid profile (decrease in HDL) and its relation to possible cardiovascular risk with continued OCA treatment

Quantification of ALP Response at 12 Months vs. 6 Months
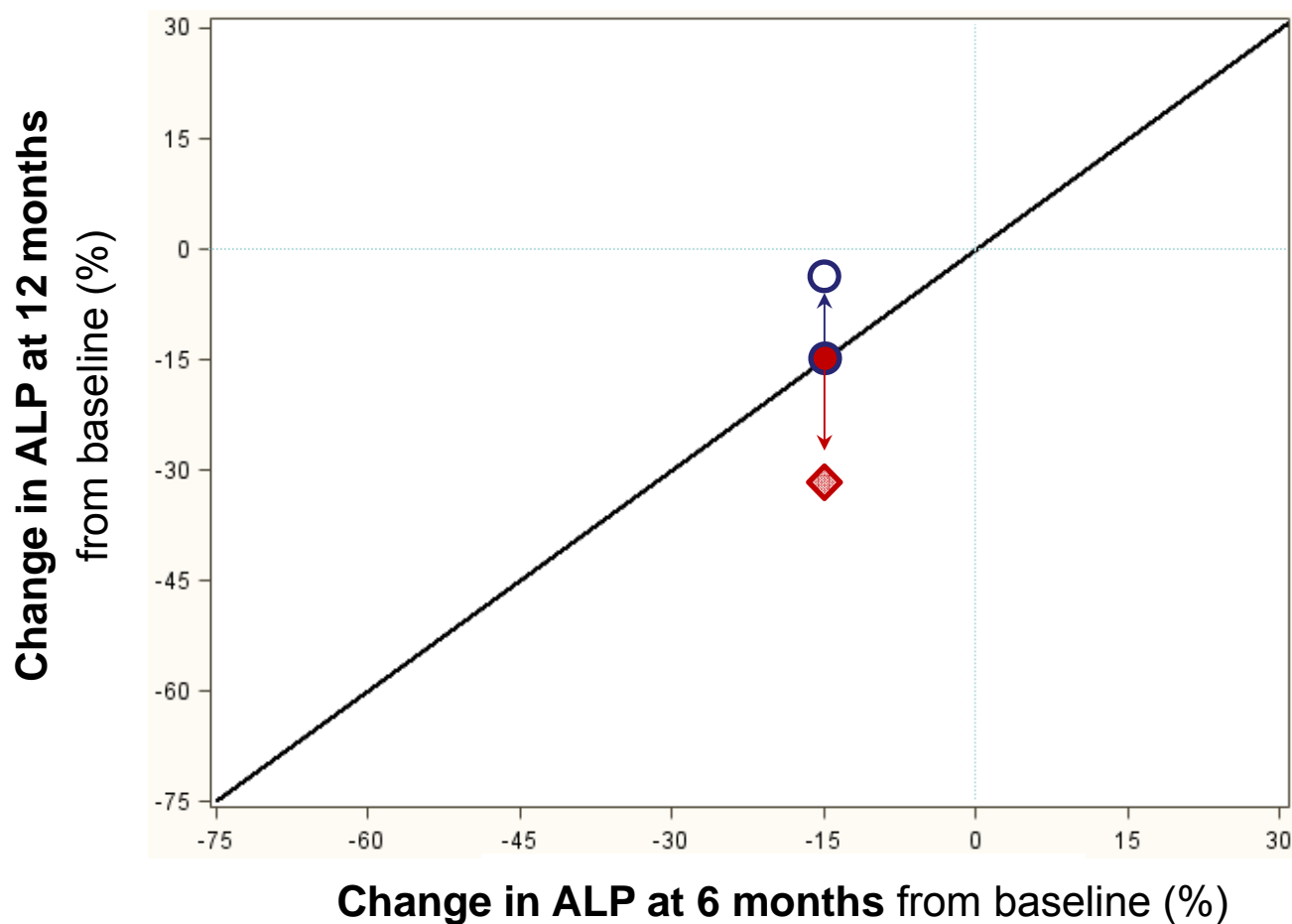
~15% Patients at 10 mg Up-titrated Dose
With No or Marginal ALP Response (Similar to Placebo?)
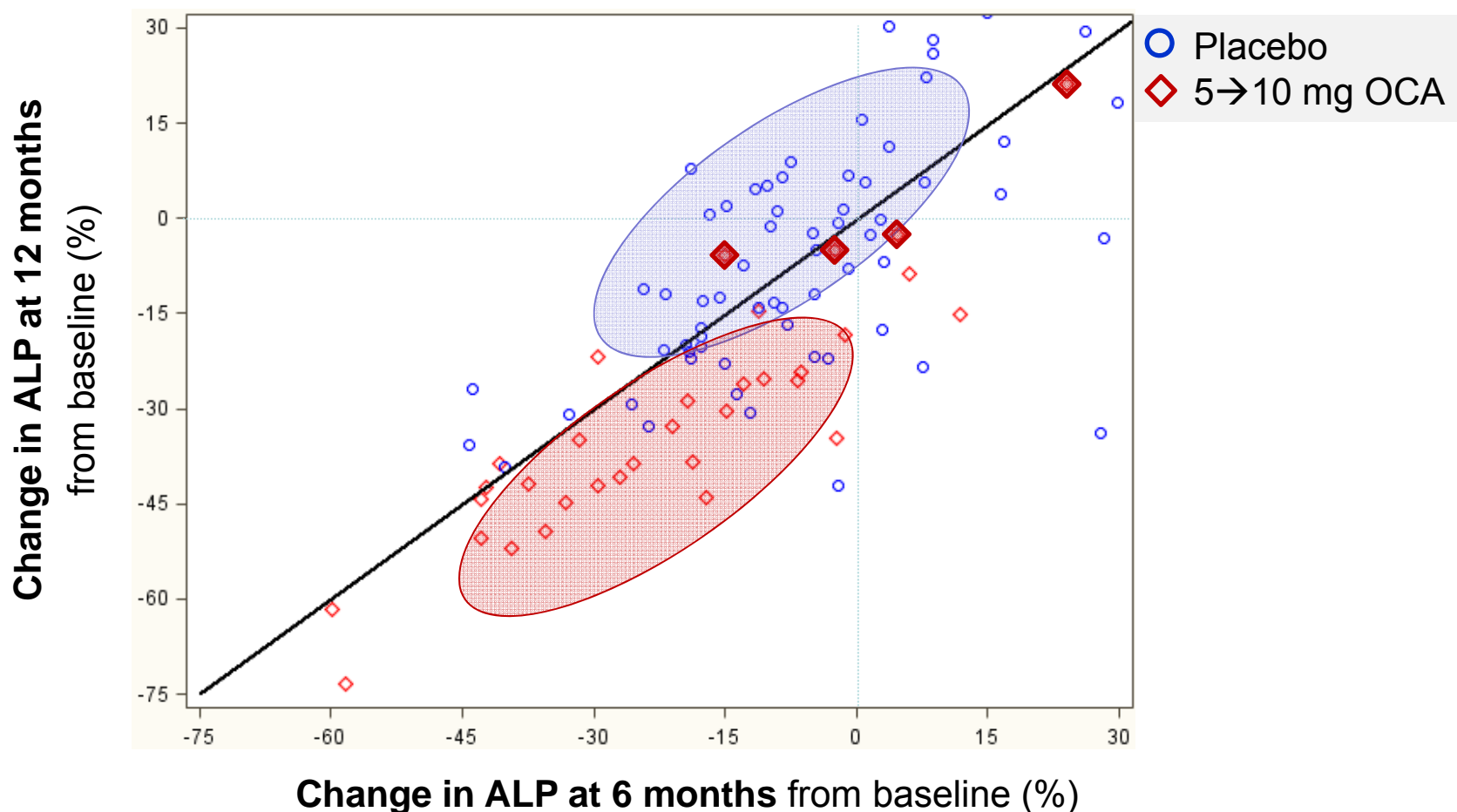
Different Temporal Patterns of ALP Response in Individuals with OCA Treatment

5 mg → 10 mg QD arm (N=33)

Up-titration to 10 mg @6M
— <15% ALP reduction
— ≥15% ALP reduction @12M
— ≥15% ALP reduction @6M
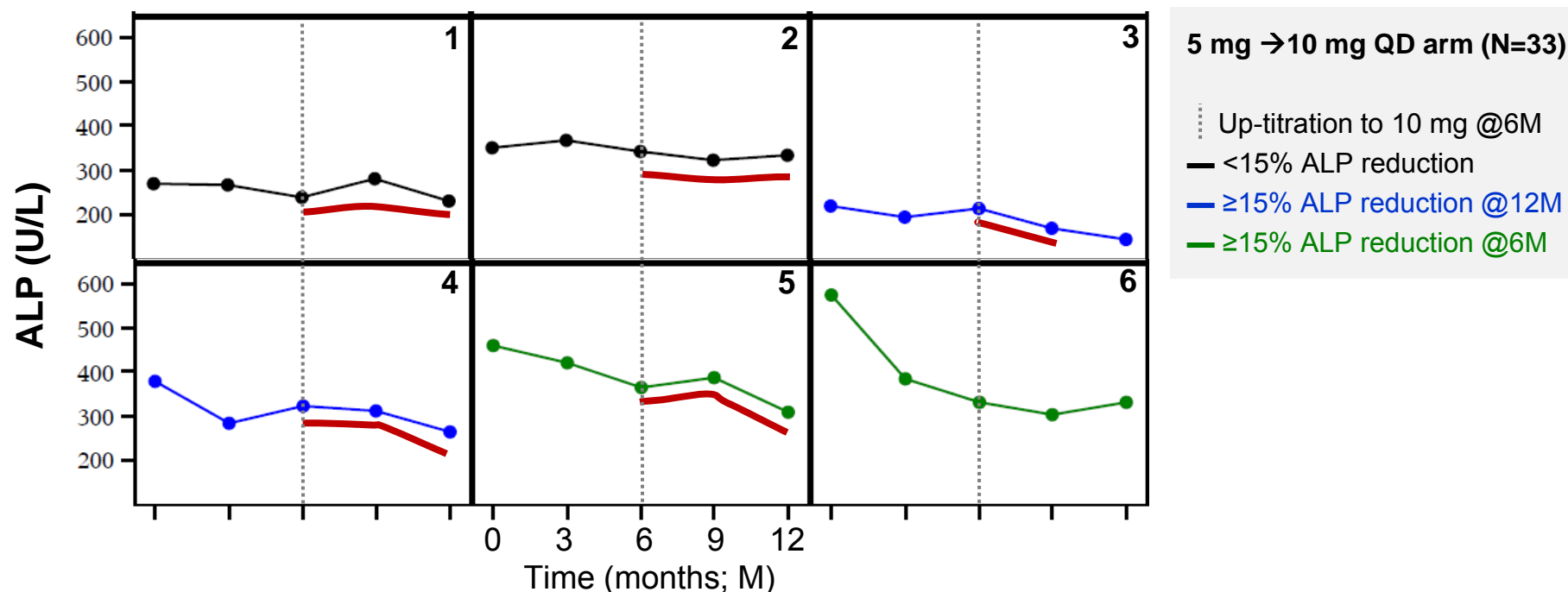
- Premature to conclude lack of response earlier than 6 months

- Physicians could potentially consider discontinuation for lack of meaningful reduction in ALP after the patient is on a stable dose for at least 6 months

Evidence from Confirmatory Trial
Could be Analyzed to Reconsider Continuation
of Therapy for Patients with No or Marginal ALP response

- Ongoing Phase 4 confirmatory trial with continued dosing of OCA for subjects with PBC - clinical endpoints (not biochemical response)

- The trial allows continued OCA dosing irrespective of biochemical response

Accelerated Approval

- Serious or life-threatening disease or condition
- Surrogate endpoint that is reasonably likely to predict clinical benefit
- Taking into account the severity, rarity, or prevalence of the condition and
- The availability or lack of alternative treatments

FDA guidance – Expedited Programs

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

Definition of a Surrogate

- A laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives.

- A biomarker that is intended to substitute for a clinical endpoint.

- Expected to predict clinical benefit (or harm or lack of benefit or harm)

Types of Surrogates

- Candidate Surrogate
  - Under evaluation for ability to predict clinical benefit

Types of Surrogates

- Candidate Surrogate
  - Under evaluation for ability to predict clinical benefit

- Reasonably likely to predict
  - Supported by mechanistic or epidemiologic rationale
  - Insufficient clinical data to validate that it does predict clinical benefit

Evidence to Support Reliance on a Surrogate Endpoint for Accelerated Approval

- Matter of judgment:
  - biological plausibility between the disease, the endpoint, and the desired effect
- Epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence
- Pharmacologic activity alone is not sufficient
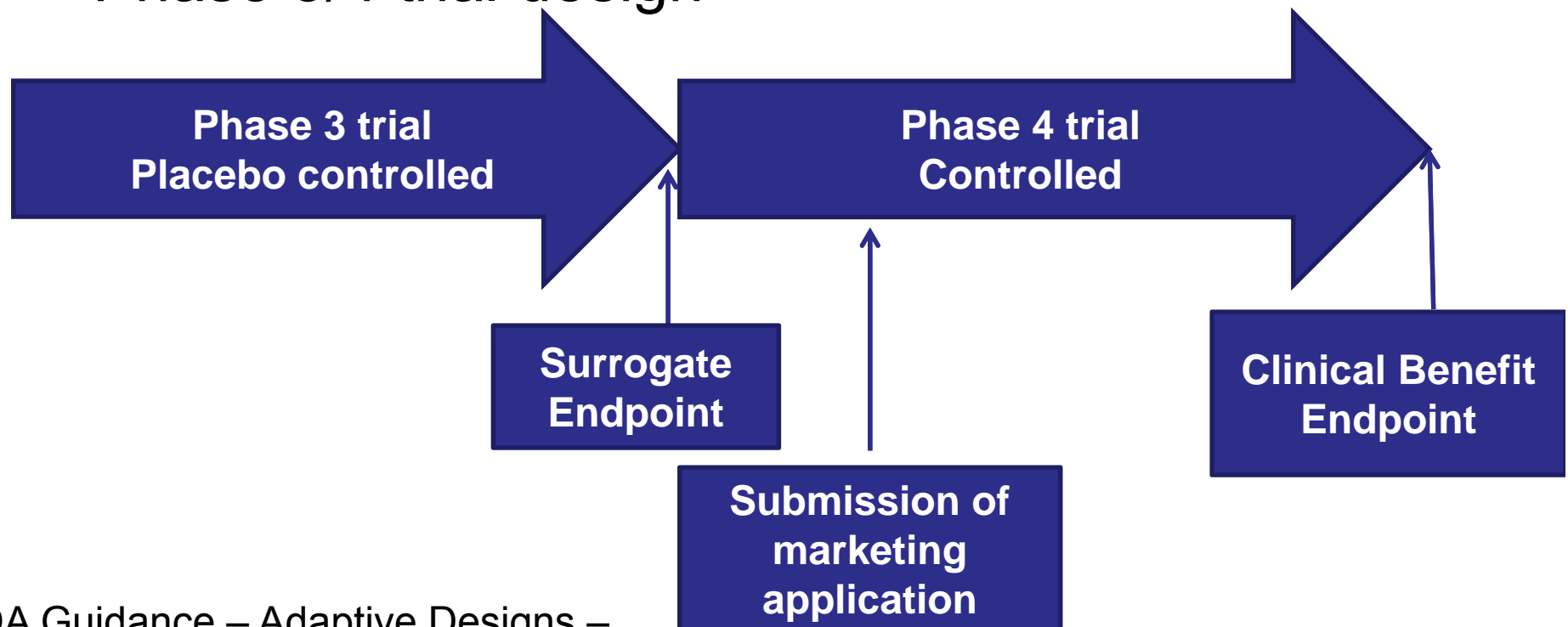
Confirmatory (Phase 4) Trial Design

- A double-blind, randomized, placebo-controlled, multicenter trial evaluating the effect of OCA on clinical outcomes in ~ 350 subjects with PBC (Trial 747-302)

- Event driven - total duration determined by the time required to accrue approximately 121 primary endpoint events
  - Estimated ~ 8 years
  - Subjects expected to have a minimum time of ~ 6 years in the trial.

Key Inclusion Criteria

- Diagnosis of PBC – (same criteria as phase 3)
- A mean total bilirubin >ULN and ≤3x ULN **and/or** a mean ALP >5x ULN
- Stable dose of UDCA or not taking UDCA
- Exclusion of other liver diseases and cirrhosis
- Model of end stage liver disease (MELD) ≤ 12

Clinical Benefit Composite Endpoint

Time to first occurrence of any of the following adjudicated events:

- Death (all-cause)

- Liver transplant

- MELD score ≥15

Clinical Benefit Composite Endpoint (continued)

- Hospitalization for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy
  - Spontaneous bacterial peritonitis
- Uncontrolled ascites
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities

Back up Slide Shown

TB Summary at Month 12
(ITT)

Time Point/Statistics	10 mg OCA (N = 73)	OCA Titration (N = 70)	Placebo (N = 73)
Baseline TB ≤ 1.0×ULN	66 (90.4%)	66 (94.3%)	66 (90.4%)
Baseline TB > 1.0×ULN	7 (9.6%)	4 (5.7%)	7 (9.6%)
Baseline TB ≤ 1.0×ULN	n=66	n=66	n=66
Month 12 TB ≤ 1.0×ULN [1]	55 (83.3%)	60 (90.1%)	56 (84.4%)
Month 12 TB > 1.0×ULN [1]	3 (4.5%)	0	7 (10.6%)
Month 12 TB missing [1]	8 (12.1%)	6 (9.1%)	3 (4.5%)
Baseline TB > 1.0×ULN	n=7	n=4	n=7
Month 12 TB ≤ 1.0×ULN [2]	5 (71.4%)	2 (50.0%)	1 (14.2%)
Month 12 TB > 1.0×ULN [2]	0	2 (50.0%)	6 (85.7%)
Month 12 TB missing [2]	2 (28.6%)	0	0

Source: Statistical Reviewer's Table.
Note: Denominators for percentages are N.
[1]: The denominator for this calculation is the number of patients with TB ≤ 1.0×ULN at Baseline.
[2]: The denominator for this calculation is the number of patients with TB > 1.0×ULN at Baseline.